SUPPORT FOR THE AMENDMENTS

Claims 1, 2, 4-8, 11-17, and 23-38 were previously canceled.

Claim 3 has been amended.

The amendment to Claim 3 is supported by the claims as originally filed and the specification throughout, see for example Examples 4-6.

No new matter has been added by the present amendments.

REMARKS

Claims 3, 9, 10, and 18-22 are pending in the present application.

At the outset, Applicants wish to thank Examiner Tsay and Examiner Rao for the helpful and courteous discussion with their undersigned representative on October 21, 2010. During this discussion several amendments and arguments to address the outstanding rejections were discussed. Applicants affirm the Examiner's summary of the discussion presented in the Interview Summary mailed October 26, 2010. The content of this discussion is reflected in and expanded upon in the following remarks. Reconsideration of the outstanding rejections is requested.

The rejections of: (a) Claims 3, 18, and 22 under 35 U.S.C. §103(a) over Himmelspach et al, (b) Claims 19-21 under 35 U.S.C. §103(a) over Himmelspach et al, and (c) Claims 9-10 under 35 U.S.C. §103(a) over Himmelspach et al, are respectfully traversed.

In the outstanding Office Action, the Examiner has maintained the rejections over Himmelspach et al. Applicants disagree for the reasons of record in the response filed May 14, 2010, which appear to be unappreciated by the Examiner. Specifically, Himmelspach et al do not disclose the Asn-229 of the native human factor X and the scope defined by the Gly_{228}-R6-R5-R4-R3-R2-Arg_{234}-R1 embraces thousands of possible sequences only one of which would closely approximate the sequence of SEQ ID NO: 9. However, Himmelspach et al do not disclose or suggest how to modify even this approximation of SEQ ID NO: 9 to arrive at the claimed replacement of the activation site of native factor X, much less provide any reasonable expectation of the results in so doing. Accordingly, Applicants submit that the Examiner has failed to provide a *prima facie* case of obviousness over Himmelspach et al.

Further, even where a *prima facie* case of obviousness is found, the evidence in the specification coupled with the Declaration under 37 C.F.R. §1.132 executed by Mr. Bernard Le Bonniec ("the Le Bonniec Declaration") filed May 14, 2010, is sufficient to overcome this rejection. In particular, the Le Bonniec Declaration shows that the claimed human factor X analogue according to the present invention *does provide extraordinary and unexpected* results, which is sufficient to rebut even a *prima facie* case of obviousness (see MPEP §2144.09). In particular, the activated form of the claimed factor X analogue:

- provides a high amidolytic activity;
- interacts with factor Va and activate prothrombin;
- has a higher half time than native activated factor X;
- has a procoagulant activity; and
- establishes an autoamplification of thrombin generation.

Applicants thank Examiner Tsay and Examiner Rao for the recognition of the foregoing argument and evidentiary showing during the discussion with their undersigned Representative on October 21, 2010. Applicants also wish to thank the Examiners for the suggested amendment to Claim 3 to include language involving the improved results relative to the wild-type. Consistent with this recommendation, Applicants have amended Claim 3 as follows:

> 3. (Currently Amended) A human factor X analogue, wherein the sequence Leu-Thr-Arg-Ile-Val-Gly (SEQ ID NO: 1) of the activation site of native factor X is replaced with the sequence Val-Pro-Arg-Ala-Val-Gly (SEQ ID NO: 9),
>
> wherein said human factor X analogue has at least one of the following enhancements compared to the native factor X:
>
> provides a high amidolytic activity;
> interacts with factor Va and activate prothrombin;
> has an increased half time than native activated factor X;
> has procoagulant activity; and/or
> establishes autoamplification of thrombin generation.

In view of the foregoing amendment, Applicants again submit the following arguments with respect to the distinctions between the claimed invention and the disclosure of Himmelspach et al. Applicants respectfully submit that Himmelspach et al fails to disclose or suggest this specific mutation with sufficient particularity to support an obviousness rejection. Further, the fact that the claimed human factor X analogue according to the present invention *does provide extraordinary and unexpected results*, clearly rebut even a *prima facie* obviousness rejection. The extraordinary and unexpected results, which now appear in Claim 3 are:

- provides a high amidolytic activity;
- interacts with factor Va and activate prothrombin;
- has a higher half time than native activated factor X;
- has a procoagulant activity; and
- establishes an autoamplification of thrombin generation.

Applicants submit that the evidence and arguments to date clearly illustrate that among all the exemplified factor X analogues, one (GDX-AVG) provides excellent results. Indeed, the present application provides a very specific factor X analogue containing a thrombin cleavage sequence, without being prejudicial to the enzymatic activity of the activated factor X. The skilled artisan would certainly appreciate that the efficiency of cleavage is conditioned by the nature of the amino acids framing the cleavage site of factor X, and more specifically by the residues P_3-P_2-P_1-P'_1-P'_2-P'_3 of the activation site, the cleavage occurring between the residues P_1 and P'_1. The residues P'_1 to P'_3 are thus involved in the catalytic activity of factor X after activation. It is thus highly unlikely that the skilled artisan could predict the enzymatic activity of an activated factor X.

Moreover, this very specific factor X analogue of the claimed invention is not exemplified by Himmelspach et al. Himmelspach et al discloses many analogues of factor X and certainly does not motivate the skilled artisan to select the very specific analogue according to the present invention. Accordingly, for the reasons that follow, the skilled artisan would simply not be led to select the exact configuration of residues which might comply with the absolutely essential feature of the present invention, among all the possibility suggested by Himmelspach et al. As such, the claimed invention would not be obvious.

Again, Applicants remind the Examiner that Himmelspach et al disclose Factor X analogues having the generic sequence:

Gly228-R6-R5-R4-R3-R2-Arg234-R I,

wherein:

a) R1 is an amino acid selected from the group consisting of Ile, Val, Ser, Thr, and Ala,

b) R2 is an amino acid selected from the group consisting of Pro, Gly, Lys, and Arg,

c) R3 is an amino acid selected from the group consisting of Phe, Lys, Met, Gin, Glu, Ser, Val, Arg, and Pro

d) R4 is an amino acid selected from the group consisting of Asp, Ile, Ser, Met, Pro, Thr, Arg, Lys,

e) R5 is an amino acid selected from the group consisting of Asn, Lys, Ser, Glu, Ala, Gln, His, and Arg, and

f) R6 is an amino acid selected from the group consisting of Asp, Phe, Thr, Arg, Leu, and Ser.

Himmelspach et al fail to disclose or suggest a factor X analogue having the sequence Leu-Thr-Arg-Ile-Val-Gly (SEQ ID NO: 1) of the activation site of native factor X replaced with the sequence Val-Pro-Arg-Ala-Val-Gly (SEQ ID NO: 9) with sufficient specificity and the artisan would have no reason to select this factor X analogue from the extensive list of alternative factor X analogues, much less an expectation of the beneficial results flowing from the same.

Indeed, as stated above Himmelspach et al merely disclose an extensive list of alternative factor X analogues and provides a generic disclosure, which can definitely not be considered as anticipating the very specific and particular combination of substituent which characterizes the analogue of factor X according to the present application.

Applicants direct the Examiner's attention to the fact that the object of the present application is a factor X, initially with a native activation site, in which said activation site is mutated between the position 232 and 237.

The native sequence of the activation site of factor X comprises the sequence:

Gly_{228}-Asn_{229}-Asn_{230}-Asn_{231}-Leu_{232}-Thr_{233}-Arg_{234}-Ile_{235}-Val_{236}-Gly_{237}

The factor X according the invention is mutated so that the sequence Leu_{232}-Thr_{233}-Arg_{234}-Ile_{235}-Val_{236}-Gly_{237} of the native activation site of factor X is replaced with the sequence Val_{232}-Pro_{233}-Arg_{234}-Ala_{235}-Val_{236}-Gly_{237}.

The factor X analogue according to the present invention thus comprises, in its activation site, the sequence:

Gly_{228}-Asn_{229}-Asn_{230}-Asn_{231}-**Val_{232}-Pro_{233}-Arg_{234}-Ala_{235}-Val_{236}-Gly_{237}**

The Examiner alleges that Himmelspach et al disclose a factor X analogue comprising the sequence:

Gly_{228}-**$R6_{229}$**-$R5_{230}$-$R4_{231}$-Val_{232}-Pro_{233}-Arg_{234}-Ala_{235}-Val_{236}-Gly_{237}

Himmelspach et al claim in column 83 that:

- R4 is an amino acid selected from the group consisting of Asp, Ile, Ser, Met, Pro, Thr, Arg, Lys. Nevertheless, Himmelspach et al also disclose at column 6 that "R4= Asn, Asp, Ile, Ser, Met, pro, Thr, Lys or Arg".
- R5 is an amino acid selected from the group consisting of Asn, Lys, Ser, Glu, Ala, Gln, His, and Arg.

- **R6** is an amino acid selected from the group consisting of Asp, Phe, Thr, Arg, Leu, Ser.

Therefore, Himmelspach et al does not disclose the presence of Asparagine (Asn) at position 229 (amino acid R6).

Accordingly, the factor X analogue according to the invention certainly does not fall within the breath of the scope of compounds embraced by Himmelspach et al.

In addition, there is no incitation in Himmelspach et al that might lead the skilled artisan to the replacement of the native activation site of factor X with the specific sequence:

Val-Pro-Arg-Ala-Val-Gly.

The present application provides a very specific factor X analogue containing a thrombin cleavable sequence, without being prejudicial to the enzymatic activity of the activated factor X.

It is indeed reminded that the efficiency of cleavage is conditioned by the nature of the amino acids framing the cleavage site of factor X, and more specifically by the residues **P_3-P_2-P_1-P'_1-P'_2-P'_3** of the activation site, the cleavage occurring between the residues P_1 and P'_1.

The residues P'_1 to P'_3 are involved in the catalytic activity of factor X after activation.

Applicants remind the Examiner that, as in all serine protease, the N-terminal residues of the catalytic chain of activated factor X (including residues P'_1 to P'_3) are involved in the enzymatic activity.

The skilled artisan is acutely aware that it is not possible to predict the enzymatic activity of an activated factor X. It was thence not obvious for the skilled artisan to select the exact configuration of residues which might comply with this absolutely essential feature of the invention.

As shown in the example of the present application, the inventors surprisingly discovered that substitution in the factor X sequence, at positions P_2-P_1-P'_1 of the sequence TR-I with the sequence PR-A makes it possible to obtain factor X analogues which can be effectively cleaved by thrombin.

In addition, the inventors discovered that this cleavage generates an activated factor X with a catalytic activity compatible with a normal physiological functions and having a longer half life than native activated factor X.

Moreover, the Examiner is reminded that "Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness." No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987)" Thus, Applicants further submit that the Examples of the present application as supported by the enclosed Declaration under 37 C.F.R. §1.132 executed by Mr. Bernard Le Bonniec ("the Le Bonniec Declaration"), as presented herein below, are sufficient to overcome a *prima facia* case of obviousness.

a. Paragraph 6 of the Le Bonniec Declaration and in Examples 1 and 4 of the specification show that the analogue according the invention is cleaved by thrombin and generates amidolytic activity

In Example 1, beginning on page 9 of the specification, the construction of expression vectors for factor X analogoues was disclosed. Specifically, several analogues of factor X were produced, which are as follows (see Table I on page 10 of the specification):

	Factor X analogue	**Sequence P_3-P_2-P_1-P'_1-P'_2-P'_3**
SEQ ID No 7	GDX-IVG	VPR-IVG
SEQ ID No 8	GDX-IFG	VPR-IFG
SEQ ID No 9	GDX-AVG	VPR-AVG
SEQ ID No 10	GDX-IFR	VPR-IFR
SEQ ID No 11	GDX-SVG	VPR-SVG
SEQ ID No 12	GDX-SFR	VPR-SFR

In Example 4 of the present application, the inventors evaluated the rate of cleavage of the factor X analogues by thrombin, depending on whether or not this cleavage generates a detectable amidolytic activity. Those experiments made also possible the measurement of the amidolytic activity generated by the activated factor X analogues.

The experiment is a Michaelis Menten kinetics experiment, wherein:

- **K_m** is a constant that is equal to the substrate concentration at which an enzyme reaction proceeds at half the maximum velocity and is associated with the affinity of the enzyme (thrombin) for substrate (the zymogen derived from factor X) ;
- **k_{cat}** gives a direct measure of the catalytic production of product under optimum conditions ; and
- **k_{cat}/K_m** represent a measure of enzyme efficiency.

The inventors thus measured the rate constant which is directly proportional to the specificity constant (k_{cat}/K_m) of the enzyme (thrombin) for its substrate (the zymogen derived from factor X).

Table V of the present application (see page 21) puts in light the following facts:

- GDX-SVG, GDX-IVG, GDX-IFG and GDX-IFR are cleaved by thrombin but

the reaction is too slow for it to be possible to estimate the value of the k_{cat}/K_m ;

- GDX-SFR analogue is cleaved very rapidly but does not generate detectable amidolytic activity ($k_{cat}/K_m=4.10^3\ M^{-1}.s^{-1}$) ; and
- GDX-AVG analogue is cleaved by thrombin and has readily detectable amidolytic activity ($k_{cat}/K_m=1.10^2\ M^{-1}.s^{-1}$).

This experiment corroborates the fact that VPR-SFR is highly favorable for cleavage by thrombin as described in the previous art.

Moreover, this experiment clearly evidences that VPR-AVG analogue is cleaved by thrombin, in a less extend than VPR-SFR, but surprisingly provide a higher amidolytic activity than the others factor X analogues.

b. Paragraph 7 of the Le Bonniec Declaration and in Example 5 of the specification show that the activated form of GDX-AVG analogue interacts with factor Va

Applicants evaluated in Example 5 of the present application the activation of prothrombin (which is naturally activated by factor Va and activated factor X).

This experiment clearly illustrates the fact that the addition of factor Va restore the catalytic activity of the activated form of GDX-AVG analogue. In addition, this experiment shows that factor Va does not provide such results with any of the others factor X analogues.

This indisputably indicates that the activated form of GDX-AVG analogue interacts with factor Va, and thus activate prothrombin.

c. Paragraph 8 of the Le Bonniec Declaration and in Example 1 of the specification show that the activated form of GDX-AVG analogue has a higher half life than its native homologue

In Example 5, Applicants determined the ability of each activated form of the factor X analogues to form a stable covalent complex with antithrombin. The inventors therefore determine the k_{on} of the interaction of antithrombin with the activated forms of the factor X analogue.

Physiologically, antithrombin is an inhibitor of the activated form of factor X and the value of its k_{on} for the interaction with activated form of factor X is about 10^4 $M^{-1}.s^{-1}$.

In this experiment, a lower value of the k_{on} of a factor X analogue suggests that its interaction with antithrombin is less effective, and thus that said analogue remains active for longer.

The results of this experiment are summarized in Table IX of the present application (see page 36):

- in absence of heparin, the values of k_{on} of the antithrombin for the activated form of GDX-AVG analogue is about 10 $M^{-1}.s^{-1}$, i.e. more than 1000 times less than that of its non mutated homologue (k_{on}=1.2.10^4 $M^{-1}.s^{-1}$), and more than 10 to 100 times less than the k_{on} values of the others factor X analogues; and
- in presence of heparin, the value of the k_{on} of the antithrombin for the activated form of GDX-AVG (k_{on}=3.01.10^2 $M^{-1}.s^{-1}$) is far lower than for the others factor X analogues.

This observation undoubtedly indicates that, after activation, the GDX-AVG analogue remains active for longer than its non-mutated homologue, which prolong the procoagulant action of the analogue and therefore considerably reinforce its anti-haemophilic properties.

To confirm this hypothesis, Applicants determined the plasma half life of the activated form of the factor X analogues by measuring their residual activity after incubation for a varying amount of time in a pool of normal human plasmas.

The results are summarized in Table X of the present application (see page 38):

- in presence of heparin, the half life of activated GDX-AVG analogue is about 5 minutes and 30 seconds, whereas the half lives of the others analogues are less than 30 seconds;
- in the absence of heparin, the half life of the activated form of GDX-AVG analogue is notably extended and is about 55 times longer that the others activated factor X analogues.

Those outstanding observations would clearly not have been obvious for the skilled artisan, on the basis of his general knowledge or in view of the teachings of Himmelspach et al.

d. Paragraph 6 of the Le Bonniec Declaration and in Example 6 of the specification show that the activated form of GDX-AVG analogue has a procoagulant activity

Applicants tested the procoagulant activity of the activated forms of the factor X analogues. The procoagulant activity of the factor X analogues is compared with that of the normal homologue lacking Gla domain (GD-FX).

Table XI of the present application (see page 40) shows that the activated form of GDX-AVG analogue shortens the clotting time as much as the activated form of the GD-FX analogue, which is not true for the other activated factor X analogues.

This result corroborates the fact that the GDX-AVG analogue clearly has a procoagulant action, unlike the others factor X analogues.

This result is confirmed by Fig. 4 of the present application which compares the procoagulant effect of the GDC-AVG analogue with the GD-FX analogue in factor VIII-depleted (4A) or factor IX-depleted (4B) plasma.

Fig. 4 shows that in the presence of GDX-AVG analogue, the clotting time is shorter than in presence of GD-FX, which undeniably confirm that GDX-AVG analogue is more active than GD-FX analogue.

The fact that GDX-AVG analogue is more active than the GD-FX indicates that an amplification of thrombin generation has indeed taken place in the presence of GDX-AVG.

The inventors have in fact shown in Example 5 that the GDX-AVG analogue lead to a production of at least 26 times more activated forms of factor X.

As summarized in paragraph 10 of the Le Bonniec Declaration, Applicants have clearly shown that:

1) The GDX-AVG analogue of factor X is efficiently cleaved by thrombin, resulting in the activated form of GDX-AVG analogue;

2) the activated form of GDX-AVG analogue provides a high amidolytic activity;

3) the activated form of GDX-AVG analogue interacts with factor Va and activate prothrombin;

4) the activated form of GDX-AVG analogue has a higher half time than native activated factor X;

5) the activated form of GDX-AVG has a procoagulant activity; and

6) the activated form of GDX-AVG analogue establishes an autoamplification of thrombin generation.

These advantages appear in Claim 3 of the presently claimed invention, which ensure the relevance of the evidence of record to the claims as currently presented.

Moreover, in view of the foregoing evidence, in paragraph 11 of the Le Bonniec Declaration, the declarant concludes:

> The foregoing evidence clearly establishes that the present invention of an analogue of factor X which has the unexpected result of bypassing the deficient steps of the clotting cascade. This invention was borne by overcoming the drawbacks of the therapeutic approaches in place prior to

the present invention but also establish auto-amplification of thrombin generation in subject suffering from haemophilia. There is no disclosure or suggestion in Himmelspach et al (US 6,573,071) to select the very specific analogue with a sequence VPR-AVG in the activation peptide, among all factor X analogues disclosed therein. As such, there is nothing expected about the foregoing results when referring to Himmelspach et al (US 6,573,071).

Accordingly, Applicants submit that it would not be obvious for the skilled artisan to identify which analogue of factor X might comply with the above mentioned characteristics. As such, Himmelspach et al fails to render the presently claimed invention obvious.

Withdrawal of these grounds of rejection is requested.

Applicants respectfully submit that the above-identified application is now in condition for allowance. Early notification to this effect is earnestly solicited.

Respectfully submitted,

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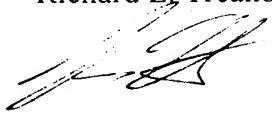

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